of infusion is for at least 96 hours.

11. (New) The method according to claim 10, further wherein said infusion of step (b) is continuous over said 96 hour period.

REMARKS

In this Amendment, Applicants have cancelled claim 2 without prejudice, have amended claims 1, 3 and 4, and have added new claims 5-11. It is respectfully submitted that no new matter has been added in the amended and new claims.

Support for the amendment to claim 1 and for the new claims is found in the instant specification at page 5, lines 10-12, page 7, lines 17-21, and at page 9, lines 1-2, lines 6-8, and lines 20-29, as well as in the claims as originally filed.

Consideration of the amended and new claims is respectfully requested at the time of examination.

35 U.S.C. § 103

35 U.S.C. § 103 over Rowinsky et al.

Claims 1-4 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Rowinsky et al.

The Examiner indicates that the claims are drawn to 35 mg of taxol per m^2 for 24 hours and that Applicants are using the above for 96 hours. The Examiner concludes that 35 x 3 is 105 mg/m^2 for 96 hours, and alleges that a showing is needed to compare 200 mg/m^2/24 hours vs. 105 mg/m^2/96 hours. For correctness, Applicants note that over 96 hours, the maximum dose of taxol is 140 mg/m^2, rather than 105 mg/m^2, as calculated by the Examiner.

Applicants traverse the rejection.

To provide background for Applicants' grounds that the reference of Rowinsky et al. does not make the presently claimed invention obvious, Applicants respectfully submit that almost all therapeutic drug regimens and treatment protocols, including drug dosages, result from a considerable amount of scientific investigation, controlled study, and clinical and medical evaluation. Drug dosing schedules result from individualized testing and adjustment, as well as from a variety of clinical and medical assessments, often including interactions with other co-administered drugs and/or pretreatments.

Although data derived from previous clinical and/or medical studies related to the treatment of specific types of diseases form a basis upon which clinicians may develop their own drug therapy protocols, previous studies do not make obvious those dosage and treatment regimens which are newly-found to be effective against *different* diseases. It is submitted that in clinical and medical practice involving the treatment of patients via the administration of drugs and/or medicaments (i.e. subject matter pertinent to the instant invention), specific drug therapy protocols and their associated dosage regimens are defined not only by the *amount* of drug/medicament administered to the patient, but also by the *period and duration of time* that the drug/medicament are provided to the patient. These two features are intimately linked to the route and mode of administration of the agent, as well as to a number of other considerations involving the fate of drugs following their administration to patients. Some of the other considerations are discussed below. Thus, it is respectfully contended that a drug treatment and dosing schedule uniquely designed for the particular purpose described in one reference dealing with a particular disease does not make obvious a different drug treatment and dosing schedule created to deal with a different disease or diseases.

In view of the foregoing discussion, it is further submitted that the differences between Applicants' invention as claimed and the disclosure of Rowinsky et al. are striking and numerous when considered with a critical eye toward the unpredictable nature of the subject

matter to which the invention pertains.

In particular, Rowinsky et al. disclose the use of taxol to study its toxic effects in *refractory leukemias*, such as histologically documented acute nonlymphocytic leukemia, acute lymphocytic leukemia, and chronic myelogenous leukemia, at a minimum starting dose of 200 mg/m^2. This minimum dose was administered to leukemic patients as a 24-hour intravenous infusion at a minimum interval of 15 days. In the introduction of their report, Rowinsky et al. mention at Col. 2, end of the second full paragraph on page 4640, that a maximum tolerated dose (mtd) and recommended Phase II doses of taxol adminstered as a 6-hour infusion were 265 and 212 mg/m^2, respectively, and 275 and 250 mg/m^2, respectfully as a 24-hour infusion.

By contrast, the presently claimed invention is directed to taxol administered to patients afflicted with *lymphoma or breast cancer* in a range of between 17.5 to 35 mg/m^2 per 24 hours. The total number of infusion hours is disclosed to be 96, with the 96 hour infusion repeated every 21 days; therefore, over the 96 hour infusion period, the claimed treatment regimen embraces from between 70 to 140 mg/m^2 of taxol.

Applicants respectfully submit that, in the report of Rowinsky et al., the authors studied a higher dose of drug administered for a shorter period of time in an effort to decrease the toxicity of the drug in patients with refractory leukemias. A prime objective of Rowinsky et al. was to determine the maximum tolerated doses of drug and to observe the toxicities which became dose-limiting when given to leukemic patients. As evidence that Rowinsky et al. were concerned with *toxicity* as an end result, rather than the ultimate *effectiveness* of the drug regimen in treating leukemic patients, Rowinsky et al. state at the end of the Abstract on page 4640 that:

> [b]ased on this study, the maximum tolerated doses and recommended Phase II doses for taxol, limited by nonhematological toxicity and administered as a 24-h i.v. infusion to patients with refractory leukemias, are 390 and 315 mg/m^2. Phase II trials at these myelosuppressive doses are required to determine taxol's activity in the treatment of leukemias.

(Emphasis added).

Thus, Rowinsky et al. plainly teach that the efficacy of taxol in treating leukemias must be tested in other trials, and that the maximum tolerated doses of the drug are high before myelosuppression is seen. More specifically, the higher doses of taxol used by Rowinsky et al. over their specified time period had little effect on the significant remission or recovery from leukemia, as revealed in the results on page 4642, Col. 1, "Antileukemic Activity", and in Table 3, Col. 2 of Rowinsky et al. This teaching does not make obvious Applicants' claimed invention.

It is further submitted that Rowinsky et al. do not teach or contemplate Applicants' claimed invention. Applicants' *effective dose* of 70 to 140 mg/m^2 per 96 hours is simply not the same as the *maximum toxic dose* of 200 to 250 mg/m^2 per 24 hours of Rowinsky et al. Applicants' lower doses of taxol administered over a longer time period were uniquely created to accomodate their inventive taxol dosing schedule for the uses disclosed and claimed. Further, Applicants tested the efficacy of their invention to determine its operativity in treating lymphomas and breast cancer. The differences between the doses of Applicants' invention and the prior art is heightened when considered in the light of the variations and differences intrinsic to each drug therapy, clinical evaluation, and drug administration schedule for a given indication.

Aware of such variations and differences, the skilled practitioner would not directly correlate Applicants' maximum disclosed dosing regimen of 140 mg/m^2 administered over 4 days with a higher dose of 200-250 mg/m^2 delivered for only 24 hours as disclosed in Rowinsky et al. In addition, for argument's sake only, since comparison is inappropriate, the arbitrary choice of 140 mg/m^2 as Applicants' dose for comparison with the 200-250 mg/m^2 mtd of Rowinsky et al. is contrary to the teaching of Applicants' specification in which a range of from 70-140 mg/m^2 is taught.

It is clear that Rowinsky et al. provide neither the guidance nor the motivation for the skilled practitioner to make the modifications necessary to arrive at Applicants' invention. Not only are the final dosages of taxol different in the present invention versus Rowinsky et al., so are the amounts of taxol used, the dosing protocol, the time course of taxol administration, the purposes for which taxol is used, and the diseases associated with this use. Of interest to the discussion related to doses of taxol and the differences therein, a copy of page 1239 (attached as Exhibit 1) from the text The Pharmacological Basis of Therapeutics, 1990, Eds. A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor, Pergamon Press, Inc. shows that taxol doses in the art are varied and substantially different from those disclosed and claimed in Applicants' specification. Under "TAXOL", the text states that "[m]aximal doses are 30 mg/m^2 per day for 5 days or 210 to 250 mg/m^2 given once every 3 weeks.". It is clear that one dosing schedule of taxol does not necessarily make obvious another, unique and independently-arrived-at taxol dosing schedule.

As alluded to above, it is respectfully submitted that Rowinsky et al. do not teach the use of taxol for the treatment of lymphomas and breast cancer. It is further submitted that the disclosure of the toxicity of taxol, at the doses and times indicated in Rowinsky et al., do not make obvious Applicants' claimed amounts of taxol, and their patentably distinct infusion times and treatment courses to effect the remission of two distinct disease states, namely, lymphoma and breast cancer. Further, because the instant invention is especially directed to the treatment of lymphomas and breast cancer, it is distinguished from the prior art which is concerned with the use of taxol for other types of diseases, such as leukemias, melanomas, carcinomas, and other non-lymphoid or non-breast tumors. Indeed, the present specification indicates at page 9, lines 34-35 that "[n]o prior treatment of lymphoma with Taxol has been reported.".

Applicants respectfully point out additional reasons that their invention is

patentably distinct from Rowinsky et al. As known in the art and explained in the The Pharmacological Basis of Therapeutics text at Chapter 2, page 34 (attached as Exhibit 2), the sites at which a drug acts and the extent of its action are determined by the localization and the specific capacity of a cell's receptors for the drug. Since the different abnormal cells associated with leukemias, lymphomas and breast cancer will likely have different capacities for and will respond differently to interaction with taxol, the amounts of taxol that are required to achieve an effect for each type of problem must be determined empirically. Therefore, a dosage of taxol reported by Rowinsky et al. (who are dealing with leukemias and toxic doses only) does not make obvious Applicants' claimed invention.

In addition, the cells intrinsic to each type of cancer or disease indication for which taxol may be used have different characteristics with respect to their resistance to taxol due to the expression of the multidrug resistance ("mdr") gene. Thus, a dose of taxol used for a type of cancer not associated with increased expression of the mdr gene product may not be extrapolated to, and indeed does not make obvious, a dose used for other types of cancer, such as lymphoma or breast cancer, which has resistance correlated with mdr expression.

Based on the foregoing distinctions between the disclosure and teachings of Rowinsky et al. and the presently-claimed invention, it is further contended that Rowinsky et al. do not teach "applicants' (use) [sic] of taxol for 24 hours at 200-250 mg/m^2 by i.v. infusion", contrary to the Examiner's allegation in the office action dated November 27, 1992, and relied on in the present final office action dated June 7, 1993. Moreover, the difference between Rowinsky et al. and Applicants' presently claimed invention is not simply the "number of hours" of taxol infusion, also alleged by the Examiner in the November 27th office action. Given the distinctions between drug therapies from indication to indication as discussed *supra* and further *infra*, Applicants' respectfully contend that the report by Rowinsky et al. does not make obvious the instant invention as presently claimed.

Further to the discussion presented above, it is respectfully maintained that one skilled in the art cannot necessarily predict from the dose and course of treatment of a drug used for one indication, such as leukemia, the dose and course of treatment that will be operative and/or effective for another indication, such as lymphoma or breast cancer. Leukemias are defined by Webster's Medical Desk Dictionary (1986) as "acute or chronic diseases characterized by an abnormal increase in the number of white blood cells in the body tissues, with or without a corresponding increase of those in the circulating blood", lymphomas are defined as "usually malignant tumors of lymphoid tissue", while a breast cancer is a malignant tumor of potentially unlimited growth that is first found in the breast, but can expand locally by invasion, and systemically by metastasis. Thus, a taxol drug protocol using a high dose of taxol for a short time period to observe the toxicity dose limits in leukemia patients does not make obvious the instantly claimed methods designed to use a lower dose over a prolonged time period for treating lymphoma and/or breast cancer patients, since the instant invention is unique in view of the strategy of Rowinsky et al.

An additional distinction between the disclosure in the paper by Rowinsky et al. and Applicants' invention as claimed is that Applicants' infusion of taxol for the treatment of lymphomas and breast cancer targets sites different from those of patients undergoing taxol infusion in Rowinksy et al. As taught in the attached pages (Exhibit 3) from the reference text Basic and Clinical Pharmacology, 1989, fourth edition, Ed. Bertram C. Katzung, M.D., Ph.D., Appleton & Lange, the action of any drug administered *in vivo* is complex and involves pharmacodynamic (i.e. the effect of drugs on the body) and pharmacokinetic (i.e. the way in which the body handles a drug) interactions. At page 29 of the text is a schematic representation of the processes which link the administration of a drug to its eventual effects (if any). As seen by the figure, the toxicity and efficacy of a drug diverge from the clinical response, which, in turn, stems from the pharmacologic effect of the drug after a given dose is administered. It

follows that the the dose and duration of administration of a drug, i.e. taxol, depend on the type of disease being treated (i.e. the use of the drug), and that a treatment involving a dose and duration for one disease (and related diseases) does not neccessarily make obvious a treatment for a different disease (and related diseases).

Finally, it is respectfully believed that Applicants' invention satisfies two long-felt needs in the field of taxol research and treatment. First, with overwhelming numbers of individuals afflicted with lymphoma and breast cancer, a new treatment regimen with taxol is an extremely valuable asset to clinicians, oncologists, and, ultimately, to patients. Second, since taxol is in short supply at present, and its cost is still prohibitive, Applicants' patentably distinct, smaller doses of taxol, used over a longer period of infusion time with greater efficacy of treatment, would insure that the limited amount of taxol available could be administered to more patients who are in great need of its effects.

In view of the foregoing, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 103, in view of Rowinsky et al. be withdrawn.

35 U.S.C. § 112, second paragraph

Claim 1 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner alleges that the term "in excess of 24 hours" in claim 1 is indefinite in failing to recite an upper limit and indicates that correction is required.

Applicants traverse the rejection.

It is submitted that the presently claimed invention obviates the rejection, as the claimed method requires that the end point of infusing the taxol solution is reached when remission of the lymphoma or breast cancer is evidenced. Thus, the skilled practitioner clearly knows that the infusion period has ended when that claim requirement is met.

It is respectfully submitted that a broad claim is not indefinite for the purposes of 35 U.S.C. § 112, second paragraph, as long as the boundaries of the claim are capable of being understood when the claim is read in light of the specification. In other words, breadth alone is not indefiniteness. *In re Gardner*, 427 F.2d 786, 166 U.S.P.Q. 138, 140 (C.C.P.A. 1970). Applicants submit that one skilled in the art is easily able to determine the appropriate period of time for infusion of taxol (i.e. the endpoint of infusion), based on the measurement of patients' responses and remission indices as disclosed in the present specification.

Accordingly, it is believed that claim 1 now satisfies the provisions of 35 U.S.C. § 112, second paragraph. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants respectfully believe that the subject application and claims are now in condition for allowance. An action passing this case to issue is courteously urged.

Respectfully submitted,

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